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(54) Title: PEPTIDE COMPOUNDS WHICH INHIBIT METALLOPROTEINASE AND TNF LIBERATION AND THEIR THERAPEUTIC USES

(57) Abstract

Tripeptidyl derivatives having a SH or acylS group and which are amides have therapeutic utility via MMP or TNF inhibition.

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Peptide compounds which inhibit metalloproteinase and TNF liberation and their therapeutic use

Field of the Invention

This invention relates to a novel class of peptidyl derivatives, to processes for their preparation, and to their use in medicine.

Background to the Invention

Tumour Necrosis Factor (TNF) is a cytokine which is produced initially as a cell-associated 28kD precursor. It is released as an active, 17kD form (D-M Jue *et al*, (1990) Biochemistry, 29:8371-8377), which can mediate a large number of deleterious effects *in vivo*. When administered to animals or humans it causes inflammation, fever, cardiovascular effects, haemorrhage, coagulation and acute phase responses, similar to those seen during acute infections and shock states. Chronic administration can also cause cachexia and anorexia. Accumulation of excessive TNF can be lethal.

There is considerable evidence from animal model studies that blocking the effects of TNF with specific antibodies can be beneficial in acute infections, shock states, graft versus host reactions and autoimmune disease. TNF is also an autocrine growth factor for some myelomas and lymphomas and can act to inhibit normal heamatopoiesis in patients with these tumours.

Preventing the production or action of TNF is, therefore, predicted to be a potent therapeutic strategy for many inflammatory, infectious, immunological or malignant diseases. These include, but are not restricted to, septic shock, haemodynamic shock and sepsis syndrome (Mathison et al, (1988) J. Clin. Invest. 81:1925-1937; Miethke et al (1992), J. Exp. Med. 175:91-98), post ischaemic reperfusion injury, malaria (Grau et al (1989), Immunol. Rev. 112:49-70); mycobacterial infection (Barnes et al (1992) Infect. Imm. 60:1441-6), meningitis, psoriasis, congestive heart failure, fibrotic disease, cachexia, graft rejection, cancer, autoimmune disease, rheumatoid arthritis, multiple sclerosis, radiation damage, toxicity following administration of immunosuppressive monoclonal antibodies such as OKT3 or CAMPATH-1 and hyperoxic alveolar injury.

Current clinical anti-TNF strategies involve the use of corticosteroids such as dexamethasone, and the use of cyclosporin-A or FK506, which are non-specific inhibitors of cytokine gene transcription. Phosphodiesterase inhibitors such as

pentoxyfilline have been shown to be more specific inhibitors of TNF gene transcription (Endres S . (1991) Immunol. 72:56-60, Schandene *et al* (1992), Immunol. 76:30-34, Alegre ML, *et al* (1991); Transplantation 52:674-679, Bianco *et al* (1991) Blood 78:1205-1221). Thalidomide has also been shown to inhibit TNF production by leucocytes (Sampajo *et al* (1991), J. Exp. Med. 173:699-703). In experimental settings, anti-TNF monoclonal antibodies, soluble TNF receptors and soluble TNF receptor/immunoadhesins have been shown to specifically inhibit the effects of TNF action (Bagby *et al* (1991) J. Infect. Dis. 163:83-88, Charpentier *et al*. (1991) Presse-med. 20:2009-2011, Silva *et al* (1990) J. Infect. Dis. 162:421-427; Franks *et al* (1991) Infect. Immun. 59:2609-2614, Tracey *et al* (1987) Nature 330:662-664; Fischer *et al* (1992) PNAS USA in press, Lesslauer *et al* (1991) Eur. J. Immunol. 21:2883-2886, Ashkenazi *et al* (1991) PNAS USA 88:10535-10539).

It has recently been shown that the effects of TNF are mediated by two peptides, TNFα and TNFβ. Although these peptides have only 30% homology with each other, they activate the same receptors and are encoded by immediately adjacent genes. As used herein, the term tumour necrosis factor or TNF therefore means tumour necrosis factor α and peptides having a high degrees of sequence homology with, or substantially similar physiological effects to, TNFα, for example TNFβ.

One of the objectives of the present invention is to provide compounds which substantially inhibit the release of TNF from cells, and therefore may be used in the treatment of conditions mediated by TNF. Such uses include, but are not limited to, the treatment of inflammation, fever, cardiovascular effects, haemorrhage, coagulation and acute phase response, cachexia and anorexia, acute infections, shock states, graft versus host reactions and autoimmune disease.

In normal tissues, cellular connective tissue synthesis is offset by extracelluar matrix degradation, the two opposing effects existing in dynamic equilibrium. Degradation of the matrix is brought about by the action of proteinases released from resident connective tissue cells and invading inflammatory cells, and is due, in part, to the activity of at least four groups of metalloproteinases. These are the collagenases (interstitial collagenase, MMP-1; PMN collagenase, MMP-8, collagenase-3, MMP-13), the gelatinases (gelatinase A, MMP-2, 72kDa-gelatinase, Type IV collagenase; gelatinase B, MMP-9, 92kDa-gelatinase, Type IV collagenase)

the stromelysins (proteoglycanase, MMP-3, stromelysin-1, transin; stromelysin-2, MMP-10; stromelysin 3, MMP-11) and the membrane type matrix metalloproteinases (MT-1, MMP-14; MT-2, MMP-15; MT-3, MMP-16 and MT-4, MMP-17).

Normally these catabolic enzymes are tightly regulated at the level of their synthesis and secretion and also at the level of their extracellular activity, the latter through the action of specific inhibitors, such as TIMP (tissue inhibitors of metalloproteinase), which form inactive complexes with metalloproteinases, and more general proteinase inhibitors such as a_2 -macroglobulins.

The accelerated, uncontrolled breakdown of connective tissues by metalloproteinase catalysed resorption of the extracellular matrix is a feature of many pathological conditions such as rheumatoid arthritis, osteoarthritis, septic arthritis, corneal, epidermal or gastric ulceration; tumour metastasis or invasion; periodontal disease, proteinuria, coronary thrombosis associated with atherosclerotic plaque rupture and bone disease. The inhibitors claimed herein may also be useful in preventing the pathological squaelae following a traumatic injury that could lead to a permanent disability. These compounds may also have utility as a means for birth control by preventing ovulation or implantation. It can be expected that the pathogenesis of such diseases is likely to be modified in a beneficial manner by the administration of metalloproteinase inhibitors and numerous compounds have been suggested for this purpose [for a general review see R C Wahl, *et al* Ann. Rep, Med. Chem. 25, 175-184, Academic Press Inc., San Diego (1990)].

A number of small peptide like compounds which inhibit metalloproteinases have been described. Perhaps the most notable of these are those relating to angiotensin converting enzyme (ACE) where such agents act to block the conversion of the decapeptide angiotensin I to angiotensin II, a potent pressor substance. Compounds of this type are described in EP-A-0012401. Also, related mercaptoamide peptidyl derivatives have shown ACE inhibitor activity *in vitro* and *in vivo* (H N Weller *et al* (1984), Biochem Biophys. Res. Comm., 125 (1):82-89).

Compounds which have the property of inhibiting the action of metalloproteinases involved in connective tissue breakdown such as collagenase, stromelysin and gelatinase have been shown to inhibit the release of TNF both *in vitro* and *in vivo* (AJH Gearing *et al* (1994), Nature, 370:555-557; GM McGeehan

at al (1994), Nature, 370:558-561: MJ Crimmin *et al*, WO 93/20047 and WO 94/10990). All of these reported inhibitors contain a hydroxamic acid zinc binding group.

It is, therefore, a further objective of this invention to provide compounds which, in addition to inhibiting TNF release, also may inhibit the action of certain MMPs, and hence may be used in the treatment of patients who suffer from conditions mediated by TNF and/or MMPs such uses include, but are not limited to inflammation, fever, cardiovascular effects, haemorrhage, coagulation and acute phase response, cachexia and anorexia, acute infections, shock states, graft versus host reactions and autoimmune disease; and those involving tissue breakdown such as bone resportion, inflammatory diseases, dermatological conditions, tumour growth, angiogenesis and invasion by secondary metastases, in particular rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration, tumour growth, angiogenesis and invasion by secondary metastases.

Compounds that inhibit collagenase, which possess structural portions akin to those of the instant invention include those encompassed by U.S.4,511,504 issued Apr. 16, 1985; U.S. 4,568,666, issued Feb 4, 1986.

Compounds of related structure that are claimed to inhibit stromelysin (proteoglycanase) are encompassed by U.S.4,771,037, issued Sept. 13, 1988.

The applicants believe that stromelysin and collagenase inhibitors have utility in preventing articular cartilage damage associated with septic arthritis. Bacterial infections of the joints can elicit an inflammatory response that may then be perpetuated beyond what is needed for removal of the infective agent resulting in permanent damage to structural components. Bacterial agents have been used in animal models to elicit an arthritic response with the appearance of proteolytic activities. See J. P. Case *et al* (1989), J. Clin. Invest., 84:1731-40; R. J. Williams *at al* (1990), Arth. Rheum., 33: 533-41.

The applicants also believe that inhibitors of stromelysin, collagenase and gelatinase will be useful to control tumour metastasis, optionally in combination with current chemotherapy and/or radiation. See L. M. Matrisian *et al* (1986), Proc. Natl. Acad. Sci., USA, 83:9413-7; S. M. Wilhelm *et al* (1987), Ibid. 84:6725-29; Z. Werb *et al* (1989), J. Cell Biol., 109:872-889; L. A. Liotta *et al* (1983), Lab.

Invest., 49:636-649; R. Reich *et al* in Metatasis; Ciba Foundation Symposium, Wiley, Chicester, 1988, pp. 193-210.

Secreted proteinases such as stromelysin, collagenase and gelatinase play an important role in processes involved in the movement of cells during metastatic tumour invasion. Indeed, there is also evidence that the matrix metalloproteinases are over expressed in certain metastatic tumour cell lines. In this context, the enzyme functions to penetrate underlying basement membranes and allow the tumour cell to escape from the site of primary tumour formation and enter the circulation. After adhering to blood vessel walls, the tumour cells use these same metalloproteinases to pierce underlying basement membranes and penetrate other tissues, thereby leading to tumour metastasis. Inhibition of this process would prevent metastasis and improve the efficacy of current treatments with chemotherapeutics and/or radiation.

These inhibitors should also be useful for controlling periodontal diseases, such as gingivitis. Both collagenase and stromelysin activities have been isolated from fibroblasts derived from inflamed gingiva (V. J. Uitto *et al* (1981), J.Periodontal Res., 16:417-424). Enzyme levels have been correlated to the severity of gum disease; C. M. Overall *et al* (1987), J. Periodontal Res., 22:81-88.

Proteolytic processes have also been observed in the ulceration of the cornea following alkali burns (S. I. Brown *et al* (1969), Arch. Opthalmol., 81:370-373). Mercapto-containing peptides do inhibit the collagenase isolated from alkali-burned rabbit cornea (F. R. Burns *et al* (1989), Invest. Opthalmol, 30:1569-1575). Treatment of alkali-burned eyes or eyes exhibiting corneal ulceration as a result of infection with inhibitors of these metalloendoproteinases in combination with sodium citrate or sodium ascorbate and/or antimicrobials may be effective in preventing developing corneal degradation.

Stromelysin has been implicated in the degradation of structural components of the glomerular basement membrane (GBM) of the kidney, the major function of which is to restrict passage of plasma proteins into the urine (W. H. Baricos *et al* (1989), Biochem. J., 254:609-612). Proteinuria, a result of glomerular disease, is excess protein in the urine caused by increased permeability of the GBM to plasma proteins. The underlying causes of the increased GBM permeability are unknown.

but proteinases including stromelysin may play an important role in glomerular diseases. Inhibition of this enzyme may alleviate the proteinura associated with kidney malfunction.

It is suggested that inhibition of matrix metalloproteinase activity may prevent the rupturing of atherosclerotic plaques leading to coronary thrombosis. The tearing or rupture of atherosclerotic plaques is the most common event initiating coronary thrombosis. Destabilisation and degradation of the connective tissue matrix surrounding these plaques by proteolytic enzymes or cytokines released by infiltrating inflammatory cells has been proposed as a cause of plaque fissuring. Such tearing of these plaques can cause an acute thrombolytic event as blood rapidly flows out of the blood vessel. High levels of stromelysin RNA message have been found to be localised to individual cells in atherosclerotic plaques removed from heart transplant patients at the time of surgery (A. M. Henney *et al* (1991), Proc. Nat'l. Acad. Sci. USA, 88:8154-8158). Inhibition of matrix metalloproteinases by these compounds may aid in preventing or delaying the degradation of the connective tissue matrix that stabilises the atherosclerotic plaques, thereby preventing events leading to acute coronary thrombosis.

It has been recently shown in a model of congestive heart failure (CHF) in the pig, that during CHF the are marked changes in the morphological structure of the heart. Ventricular dilation and wall thinning caused by changes to the extracellular matrix results in fewer collagen connections between cardiomyocytes and less total collagen. In such an instance a weaker force of contraction leads to an inefficient ventricular operation. It is believed that specific inhibitors of matrix metalloproteinases will play a key role in stabilising the extracellular matrix and therefore be important in the treatment and/or prevention of CHF.

It has recently been shown (WO 96/0240) that inhibitors of the matrix metalloproteinases, such as collagenase and stromelysin also inhibit the formation of human soluble CD23. CD23 is a 45kDa type II integral protein expressed on the surface of a variety of mature cells, including B and T lymphocytes, macrophages, NK cells, Langerhans cells, monocytes, eosinophils and platelets (Delespesse *et al*, Adv. Immunology, 49 , 1991, 149; Grangette *et al*, J., Immunol, 143, 1989, 3580).

Several activities have been ascribed to soluble CD23 in man, all of which involve IgE regulation. Particular activities include:

i) antigen presentation

ii) IgE mediated eosinophil cytotoxicity

iii) B cell homing to lymph nodes and the spleen

iv) downregulation of IgE synthesis

Thus, overall the excessive production of soluble CD23 has been implicated in the overproduction of IgE, the hallmark of allergic diseases such as extrinsic asthma, rhinitis, allergic conjunctivitis, eczema, atopic dermatitis and anaphylaxis (Sutton et al, Nature, 366, 1993, 421). Elevated levels of soluble CD23 have also been observed in the serum of patients with chronic B lymphocytic leukaemia (Safarti *et al*, Blood, 71, 1988, 94), and in the synovial fluid of patients with rheumatoid arthritis (Chomarat *et al*, Arthritis and Rheumatism, 36, 1993, 234).

It is therefore, a further objective of the present invention to provide compounds which inhibit the formation of human soluble CD23 for the production of a medicament for the treatment or prophylaxis of disorders such as allergy and autoimmune disease in which the overproduction of soluble CD23 is implicated, such as those described above.

Recent reports suggest that new enzymes of the MMP family also mediate the shedding of adhesion molecules such as the selectins, such as L-selectin. These soluble adhesion molecules are implicated in a number of diseases including cancer, autoimmunity and in the inflammatory response. It has been proposed that once cleaved, the selectin bind to particular ligands and this accounts for their biological activity. Thus, drugs that interfere with or prevent binding of the ligands to the selectins will be useful medicaments for treating a variety of the diseases described above. Therefore, it is a yet further objective of the present invention to provide compounds which inhibit the shedding of certain adhesion molecules and thus provide the production of a medicament for the treatment or prophylaxis of disorders such as cancer, autoimmune diseases or inflammatory diseases (such as inflammatory bowel disease and multiple sclerosis).

It is also believed that specific inhibitors of gelatinase and collagenase would be useful as birth control agents. There is evidence that expression of

metalloproteinases, including stromelysin and collagenase, is observed in unfertilised eggs and zygotes and at further cleavage stages and increased at the blastocyst stage of fetal development and with endoderm differentiation (C. A. Brenner *et al* (1989), Genes & Develop., 3:848-59). By analogy to tumour invasion, a blastocyst may express metalloproteinases in order to penetrate the extracellular matrix of the uterine wall during implantation. Inhibition of stromelysin and collagenase during these early development processes should presumably prevent normal embryonic development and/or implantation in the uterus. Such intervention would constitute a novel method of birth control. In addition there is evidence that collagenase is important in ovulation processes. In this example, a covering of collagen over the apical region of the follicle must be penetrated in order for the ovum to escape. Collagenase has been detected during this process and an inhibitor has been shown to be effective in preventing ovulation (J. F. Woessner *et al* (1989), Steroids, 54:491-499). There may also be a role for stromelysin activity during ovulation (C. K. L. Too *et al* (1984), Endocrin., 115:1043-1050).

Collagenolytic and stromelysin activity have also been observed in dystrophic epidermolysis bullosa (A. Kronberger *et al* (1982), J. Invest. Dermatol., 79:208-211; D. Sawamura *et al* (1991), Biochem. Biophys. Res. Commun., 184:1003-8). Inhibition of metalloendoproteinases should limit the rapid destruction of connective components of the skin.

In addition to extracellular matrix comprising structural components, stromelysin can degrade other *in vivo* substrates including the inhibitors a_1-proteinase inhibitor and may therefore influence the activities of other proteinases such as elastase (P. G. Winyard *et al* (1991), FEBS Letts., 279,1:91-94). Inhibition of the matrix metalloendoproteinases may potentiate the antiproteinase activity of these endogenous inhibitors.

From recent publications it is evident that several new enzymes of the MMP family have been identified, some of which may be important in disease. Collagenase 3, an enzyme found in breast carcinoma tissue may have utility in breast cancer (JMP Freije *et al* (1994), J. Biol. Chem., 269 (24): 16766-16773) and other disease states, such as arthritis, whilst MT-MMPs, other members of the MMP family have been shown to be key enzymes in the activation of gelatinase A (H Sato

et al (1994), Nature, 370:61-65). Gelatinase A is an important enzyme in the growth and metastasis of tumours (such as defined above).

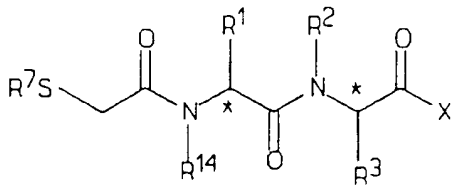
The degradation of β-Amyloid Precusor Protein (APP) has been shown to generate amyloid plaques, a major constituent of the senile plaques, found in patients with Alzheimers Disease (AD). Two recent publications have identified metalloproteinase enzymes that cleave APP to the amyloid plaque (CR Abraham *et al* (1994), Biochemistry, 33:192-199; G Huber *et al* (1994), Biochem. Biophys. Res. Comm., 201 (1):45-53).

As appreciated by those of skill in the art, the significant proportion of homology between these new enzymes and other MMPs leads to the possibility that a compound that inhibits one enzyme may to some degree inhibit these new enzymes. Therefore, inhibitors encompassed in this invention may be useful in the diseases in which these new enzymes are implicated.

SUMMARY OF THE INVENTION

The invention encompasses novel mercaptoalkylpeptidyl compounds of formula (I) which are useful inhibitors of matrix metalloproteinase and/or TNF mediated diseases including degenerative diseases (such as defined above) and certain cancers.

In a first aspect of the invention there is provided a compound of general formula (I)



(I)

Wherein:

R^1 is a C_{1-6} alkyl, C_{2-6} alkenyl, (C_{1-6} alkyl) aryl, aryl, (C_{1-6} alkyl) heteroaryl, heteroaryl or C_{1-6} alkyl AR^9 group where A is O, NR^9 or $S(O)_m$ where m=0-2, and

[illegible] alkyl, heteroaryl, alkyl aryl, alkyl heteroaryl, if A = NR^9 the R^9 groups may be the same or different

R^2 is hydrogen or a C_{1-6} alkyl group;

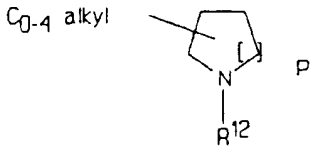
R^3 is a $[Alk]_nR^6$ group where Alk is a C_{1-6} alkyl or C_{2-6} alkenyl group and n is zero or an integer 1;

X is a group NR^4R^5 where R^4 is hydrogen, aryl, heteroaryl, C_{1-6} alkyl-heteroaryl, cyclo(C_{3-6})alkyl, C_{1-6} alkyl-cyclo(C_{3-6})alkyl, heterocyclo(C_{3-6})alkyl or C_{1-6} alkyl-heterocyclo(C_{3-6})alkyl, or the group C_{1-6} alkyl optionally substituted by amino (NH_2), aryl, arylamino, protected amino, di (C_{1-6} alkyl) amino, mono (C_{1-6} alkyl) amino, CO_2H, protected carboxyl, carbamoyl, mono (C_{1-6} alkyl) carbamoyl, di (C_{1-6} alkyl) carbamoyl, and R^5 is hydrogen or a C_{1-6} alkyl group; NR^4R^5 may also form a ring such as in a pyrrolidino, piperidino or morpholino group.

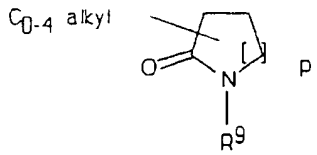
R^7 is hydrogen or the group $R^{10}CO$ where R^{10} is a group C_{1-4} alkyl, C_{1-4} alkyl-aryl, C_{1-4} alkyl- heteroaryl, cyclo (C_{3-6}) alkyl, C_{1-4} alkyl-cyclo (C_{3-6}) alkyl, C_{2-6} alkenyl, C_{2-6} alkenyl-aryl, aryl or heteroaryl;

R^{14} is OH, NH_2, OR^8, NHR^8 or R^8;

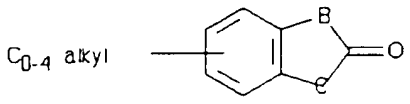
R^8 is aryl (optionally substituted with R^{11}), heteroaryl (optionally substituted with R^{11}), C_{1-4} alkyl (optionally substituted with R^{11}), C_{1-4} alkyl-aryl (optionally substituted with R^{11}), C_{1-4} alkyl-heteroaryl (optionally substituted with R^{11}), cyclo (C_{3-6}) alkyl (optionally substituted with R^{11}), cyclo (C_{3-6}) alkenyl (optionally substituted with R^{11}), C_{1-4} alkyl-cyclo (C_{3-6}) alkyl (optionally substituted with R^{11}), the groups



or



where p=1-2, or the group



where B and C may be selected from the groups O,S,$C(R^9)_2$, or NR^9 and these may be the same or different;

R^6 is an optionally substituted cyclo (C_{3-6}) alkyl, cyclo (C_{3-6}) alkenyl, C_{1-6} alkyl, aryl, C_{1-6} alkoxy aryl, benzyloxyaryl, heteroaryl, COR^9, C_{1-3} alkyl-aryl, C_{1-3} alkyl-heteroaryl, alkyl-CO_2R^9, C_{1-6} alkyl-NHR^9, AR^9, CO_2R^9, $CONHR^{10}$, $NHCOR^{10}$, $NHCO_2R^{10}$ or $NHSO_2R^{10}$, an amidine or guanidine group;

R^{11} is a SR^7, COR^{13}, SO_2R^9 (when R^9 is not H), $SO_2N(R^9)_2$, $N(R^9)_2$, NR^9R^{12}, OR^9, COR^9, phthalimido or succinimido group.

R^{12} is hydrogen or a COR^9, CO_2R^9, $CONHR^9$ or SO_2R^9 (where R^9 is not H) group;

R^{13} is a OH, OC_{1-4} alkyl, $O(C_{1-4}$ alkyl) aryl, $N(R^9)_2$ (in which R^9 is the same or different);

and the salts, solvates and hydrates thereof.

Preferred compounds of the invention include those in which, independently or in any combination have:

R^1 is C_{1-6} alkyl or C_{1-4} alkyl-AR^9 where A is $S(O)_m$,NR^9, or O and m=0,1 or 2, and R^9 is H, C_{1-4} alkyl, aryl or heteroaryl;

R^2 is H or C_{1-4} alkyl;

R^3 is $[Alk]_nR^6$ where n=0 or 1, Alk is C_{1-4} alkyl and R^6 is C_{1-4} alkyl, C_{1-3} alkyl-aryl, C_{1-3} alkyl-heteroaryl, CO_2R^9, AR^9, $CONHR^{10}$, $NHCOR^{10}$, $NHCO_2R^{10}$ or $NHSO_2R^{10}$, an amidine or guanidine group;

R^5 is H;

R^4 is H, C_{1-6} alkyl, aryl, heteroaryl, C_{1-6} alkyl-aryl, C_{1-6} alkyl-heteroaryl or C_{1-4} alkyl-$N(R^9)_2$;

NR^4R^5 may form a 5-7 membered ring such as a pyrrolidine, piperidine or morpholine;

R^7 is H or $R^{10}CO$ where R^{10} is C_{1-4} alkyl or aryl;

R^8 is C_{1-4} alkyl-R^{11}, C_{1-4} alkenyl-R^{11}, cyclo(C_{3-6})alkyl-R^{11} or C_{1-4} alkyl;

R^{11} is COR^{13}, NR^9R^{12}, $N(R^9)_2$, phthalimido or succinimido;

R^{12} is COR^9, CO_2R^9 (provided R^9 is not H), or SO_2R^9 (provided R^9 is not H);

R^{13} is OH, OC_{1-4} alkyl or $N(R^9)_2$;

Compounds of the invention have IC_{50} values below 50μM against the MMP enzymes and/or below 50μM in the whole cell assay of TNF inhibition.

It will be appreciated that the compounds according to the invention can contain one or more asymmetrically substituted carbon atoms, for example those marked with an asterisk in formula (I). The presence of one or more of these asymmetric centres in a compound of formula (I) can give rise to stereoisomers, and in each case the invention is to be understood to extend to all such stereoisomers, including enantiomers and diastereomers, and mixtures including racemic mixtures thereof.

In the formulae herein, the ~ line is used at a potential asymmetric centre to represent the possibility of *R*- and *S*- configurations, the < line and the ..... line to represent a unique configuration at an asymmetric centre.

As used in this specification, alone or in combination, the term "C_{1-6} alkyl" refers to a straight or branched chain alkyl moiety having from one to six carbon atoms, including for example, methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, pentyl, hexyl and the like.

The term "C_{1-4} alkyl" refers to a straight or branched chain alkyl moiety having from one to four carbon atoms, including for example, methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl and the like.

The term "C_{2-6} alkenyl" refers to a straight or branched chain alkyl moiety having two to six carbon atoms and having in addition one double bond, of either E or Z stereochemistry where applicable. This term would include for example, vinyl, 1-propenyl, 1- and 2- butenyl, 2- methyl-2-propenyl etc.

The term "cyclo (C_{3-6}) alkyl" refers to a saturated alicyclic moiety having from three to six carbon atoms and includes for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

The term "cyclo (C_{3-6}) alkenyl" refers to an alicyclic moiety having from three to six carbon atoms and having in addition one double bond. This term would include for example cyclopentenyl or cyclohexenyl.

The term "heterocyclo (C_{4-6}) alkyl" refers to a saturated heterocyclic moiety having from three to six carbon atoms and one or more heteroatom from the group

N, O, S and includes for example azetidinyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl and the like.

There term "aryl" means an optionally substituted phenyl or naphthyl group with the substituent(s) being selected, for example, from halogen, trifluoromethyl, C_{1-6} alkyl, alkoxy, phenyl and the like.

The term "halogen" means fluorine, chlorine, bromine or iodine.

The terms "protected amino" and "protected carboxy" mean amino and carboxy groups which are protected in a manner familiar to those skilled in the art. For example, an amino group can be protected by a benzyloxycarbonyl, *tert*-butoxycarbonyl, acetyl or like groups, or in the form of a phthalimido or like group. A carboxyl group can be protected in the form of a readily cleavable ester such as the methyl, ethyl, benzyl or *tert*-butyl ester.

The term "alkoxy" refers to a straight chain or branched chain alkoxy group containing a maximum of six carbon atoms, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, *tert*-butoxy and the like.

The term "C_{0-4} alkyl" refers to a straight chain or branched chain alkoxy group containing a maximum of four carbon atoms, such as methyl, ethyl, propyl, propyl, butyl, *tert*-butyl and the like.

The term "heteroaryl" refers to aromatic ring systems of five to ten atoms or which at least one atom is selected from the group, O, N, or S and includes for example furanyl, thiophenyl, pyridyl, indolyl, quinolyl and the like.

The term "optionally substituted" refers to a group unsubstituted or substituted with a group taken from but not limited to halogen, trifluoromethyl, C_{1-6} alkyl, phenyl or a group R^{11}, where R^{11} has been defined previously, and the like.

Salts of compounds of formula (I) include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, such as hydrochlorides, hydrobromides, p-toluenesulphonates, phosphates, sulphates, perchlorates, acetates, trifluoroacetates, propionates, citrates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

Salts may also be formed with bases. Such salts include salts derived from organic or inorganic bases, for example alkali metal salts such as magnesium or

calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

When the "protected carboxy" group in compounds of the invention is an esterified carboxyl group, it may be a metabolically labile ester of formula CO_2R^{15} where R^{15} may be an ethyl, benzyl, phenethyl, phenylpropyl, a or b-naphthyl, 2,4-dimethylphenyl, 4-*tert*-butylphenyl, 2,2,2-trifluoroethyl, 1-(benzyloxy)benzyl, 1-(benzyloxy)ethyl, 2-methyl-1-propionyloxypropyl, 2,4,6-trimethylbenzyloxymethyl or pivaloyloxymethyl group.

Compounds of the general formula (I) may be prepared by any suitable method known in the art and/or by the following processes, which itself forms part of the invention.

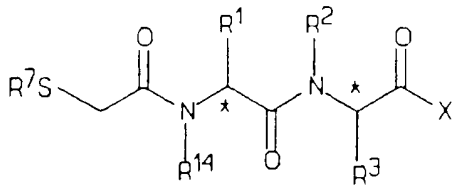
According to a second aspect of the invention, there is provided a process for preparing a compound of general formula (I) as defined above. It will be appreciated that where a particular stereoisomer of formula (I) is required, the synthetic processes described herein may be used with the appropriate homochiral starting material and/or isomers maybe resolved from mixtures using conventional separation techniques (eg. HPLC).

The compounds according to the invention may be prepared by the following process. In the description and formulae below the groups R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, A, B, C and X are as defined above, except where otherwise indicated. It will be appreciated that functional groups, such as amino, hydroxyl or carboxyl groups, present in the various compounds described below, and which it is desired to retain, may need to be in protected form before any reaction is initiated. In such instances, removal of the protecting group may be the final step in a particular reaction. Suitable protecting groups for such functionality will be apparent to those skilled in the art. For specific details see "Protective Groups in Organic Synthesis", Wiley Interscience, T W Greene, PGM Wuts.

Thus the process required for preparing compounds of general formula (I) comprises of:

deprotecting (for example by hydrolysis) a compound of general formula (II)

(II)

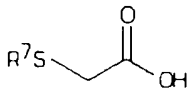


Wherein R^7 represents a suitable protecting group (eg *tert*-butyl, trityl, acetate or benzoate).

It will be appreciated that where a particular stereoisomer or formula (I) is required, this may be obtained by conventional resolution techniques such as high performance liquid chromatography. Where desired, however, appropriate homochiral starting materials may be used in the coupling reaction to yield a particular stereoisomer of formula (I). This is exemplified below.

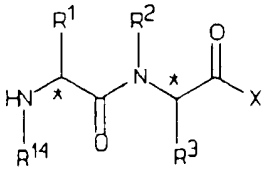
Intermediates of general formula (II) may be prepared by coupling an acid of formula (III)

(III)



Wherein R^7 is as defined above, or an active derivative thereof, with an amine of formula (IV)

(IV)

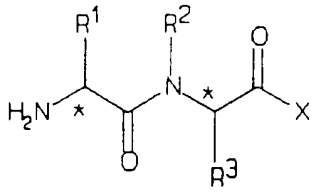


Active derivatives of acids of formula (III) include for example acid anhydrides or acid halides, such as acid chlorides.

The coupling reaction may be performed using standard conditions for amination reactions of this type. Thus, the reaction may be achieved in a solvent, for example an inert organic solvent such as an ether, eg. a cyclic ether such as tetrahydrofuran, an amide eg. a substituted amide such as dimethylformamide, or a halogenated hydrocarbon such as dichloromethane at a low temperature eg. -30°C to ambient temperature, such as -20°C to 0°C, optionally in the presence of a base, eg. an organic base such as an amine, eg. triethylamine or a cyclic amine such as *N*-methylmorpholine. Where an acid of formula (III) is used, the reaction may additionally be performed in the presence of a condensing agent, for example a diimide such as *N,N'*-dicyclohexylcarbodiimide, advantageously in the presence of a triazole such as 1-hydroxybenzotriazole. Alternatively, the acid may be reacted with a chloroformate for example ethylchloroformate, prior to reaction with the amine of formula (IV).

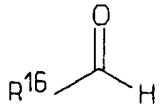
The amine of general formula (IV) may be prepared by reductive alkylation of the amine of formula (V)

(V)

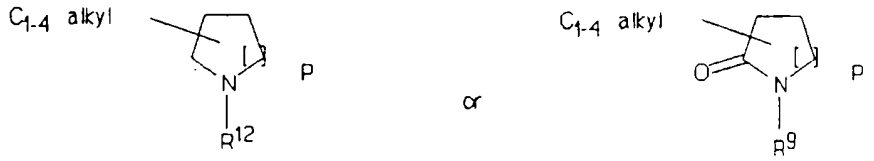


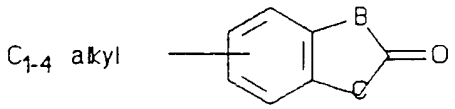
with an aldehyde of formula (VI)

(VI)



wherein R^{16} consists of C_{2-4} alkyl (optionally substituted with R^{11}), C_{2-4} alkyl-aryl (optionally substituted with R^{11}), C_{2-4} alkyl-heteroaryl (optionally substituted with R^{11}), C_{2-4} alkyl-cyclo (C_{3-6}) alkyl (optionally substituted with R^{11}), the groups





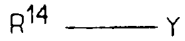
where p = 1-2, the group

where B and C may be selected from the groups O,S,$C(R^9)_2$, or NR^9 and these may be the same or different;

R^{11} is SR^7, COR^{13}, SO_2R^{13}, $N(R^9)_2$, NR^9R^{12}, OR^9, COR^9, phthalimido or succinimido;

Where R^7, R^9, R^{12}, R^{13} are described previously.

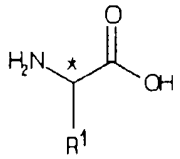
Amines of general formula (IV) may also be prepared by alkylation of the amine (V) with compounds of general formula (VII)



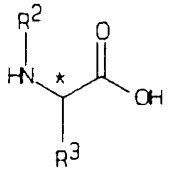
(VII)

wherein Y represents a suitable leaving group (eg. a halogen such as bromide, or an alkylsulphonate ester such as methanesulphonate).

The amine of general formula (V) may be prepared by coupling an acid of formula (VIII), or an active derivative thereof

(VIII) 

with an amine of formula (IX)

(IX) 

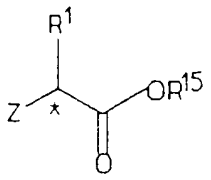
Followed by removal of any protecting groups.

Active derivatives of acids of formula (VIII) include for example acid anhydrides or acid halides such as acid chlorides as outlined earlier.

Amino acids and their derivatives as depicted by general formulae (VIII) and (IX) can be obtained in the optically pure or racemic form. In the homochiral form they provide asymmetric building blocks for the enantiospecific synthesis of compounds of general formula (I). Many of these derivatives can be readily obtained from commercially available starting materials using methods known to those skilled in the art. (See "The Practice of Peptide Synthesis" by M. Bodanszk *et al*, Springer Verlag, New York, 1984 and P.L. Durette, WO92/213460).

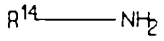
Particularly useful when R^{14} is aryl or heteroaryl, in a further extension to the present invention, amines of general formula (IV) may be prepared by nucleophilic substitution of compounds of formula (X).

(X)



where in Z represents a suitable leaving group (eg. a halide such as bromide or an alkylsulphonate ester such as trifluoromethanesulphonate) and R^{15} represents an alkyl group (such as methyl, ethyl, *tert*-butyl, benzyl etc)

with an amine of general formula (XI)

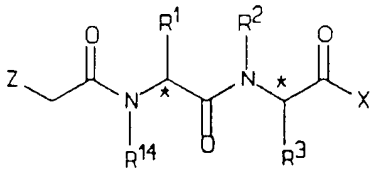


(XI)

Followed by de-esterification and coupling to an amine of formula (IX) as described previously.

Also, as a further extension to the current invention, compounds of general formula (II) may be prepared by nucleophilic substitution of compounds of formula (XII)

(XII)



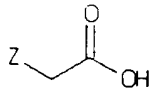
wherein Z represents a suitable leaving group as described previously, with a thiol of general formula (XIII)

XIII

Wherein R^7 represents a suitable protecting group (eg. *tert*- butyl, trityl, benzoate or acetate), using standard conditions known to those skilled in the art as exemplified by C.Campion *et al*, WO 90/9005719.

Thiols of general formula (XIII) may be obtained from commercially available starting materials using methods known to those skilled in the art. Many thiols of general formula (XIII) are also commercially available.

Compounds of general formula (XII) may be prepared by coupling an acid of general formula (XIV)



(XIV)

wherein Z is defined above (or suitably protected versions thereof) or an active derivative thereof, with an amine of formula (IV) using similar coupling conditions to those described for the preparation of compounds of formula (II).

Compounds of formula (I) may also be prepared by interconversion of other compounds of formula (I). Thus, for example, a compound of formula (I) wherein R^1 is a C_{1-6} alkyl group may be prepared by hydrogenation (using palladium on carbon in suitable solvent, such as an alcohol - eg ethanol) of a compound of formula (I) wherein R^1 is a C_{2-6} alkenyl group. A further example would include a compound of formula (I) wherein R^7 is a group R^{10} CO may be prepared by acylation (using a suitable acid chloride R^{10} COCl, in the presence of a base such as a triethylamine in a suitable solvent, such as a chlorinated solvent - eg dichloromethane) of a compound of formula (I) wherein R^7 is H.

Any mixtures of final products or intermediates obtained can be separated on the basis of the physico-chemical differences of the constituents, in a known manner, into the pure final products or intermediates, for example by chromatography, distillation, fractional crystallization, or by formation of a salt if appropriate or possible under the circumstances.

Compounds according to the invention exhibit *in vitro* inhibition of TNF release by cells. The compounds according to the invention may also exhibit *in vitro* inhibiting activities with respect to matrix metalloproteinases such as stromelysin, collagenase and gelatinase. The activity and selectivity of the compounds may be determined by use of the appropriate enzyme inhibition test, for example as described in Example A hereinafter.

This invention also relates to a method of treatment for patients (including man and/or mammalian animals raised in the dairy, meat or fur industries or as pets) suffering from disorders or diseases which can be attributed to stromelysin as previously described, and more specifically, a method of treatment involving the administration of the matrix metalloproteinase inhibitors of formula (I) as the active constituents.

Accordingly, the compounds of formula (I) can be used among other things in the treatment of osteoarthritis and rheumatoid arthritis, and in diseases and indications resulting from the over-expression of these matrix metalloproteinases such as found in certain metastatic tumour cell lines.

As mentioned above, compounds of formula (I) are useful in human or veterinary medicine since they are active as inhibitors of TNF and/or MMPs. Accordingly in another aspect, this invention concerns:

a method of management (by which is meant treatment of prophylaxis) of disease or conditions mediated by TNF and/or MMPs in mammals, in particular in humans, which method comprises administering to the mammal an effective, amount of a compound of formula (I) above, or a pharmaceutically acceptable salt thereof; and

a compound of formula (I) for use in human or veterinary medicine, particularly in the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by TNF and/or MMPs; and

the use of a compound of formula (I) in the preparation of an agent for the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by TNF and/or MMPs.

The disease or conditions referred to above include inflammatory diseases autoimmune diseases cancer, cardiovascular diseases, diseases involving tissue

breakdown such as rheumatoid arthritis, osteoarthritis, osteoporosis, neurodegeneration, Alzheimer's disease, atherosclerosis, congestive heart failure, stroke, vasculitis, Crohn's disease, ulcerative colitis, multiple sclerosis, periodontitis, gingivitis and those involving tissue breakdown such as bone resportion, haemorrhage, coagulation, acute phase response, cachexia and anorexia, acute infections, HIV infections, fever, shock states, graft versus host reactions, dermatological conditions, surgical wound healing, psoriasis, atopic dermatitis, epidermolysis bullosa, tumour growth, angiogenesis and invasion by secondary metastases, ophthalmological disease, retinopathy, corneal ulceration, reperfusion injury, migraine, meningitis, asthma, rhinitis, allergic conjunctivitis, eczema and anaphylaxis.

For the treatment of rheumatoid arthritis, osteoarthritis, and in diseases and indications resulting from the over-expression of matrix metalloendoproteinases such as found in certain metastatic tumour cell lines or other diseases mediated by the matrix metalloendoproteinases or increased TNF production, the compounds of formula (I) may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats etc, the compounds of the invention are effective in the treatment of humans.

The pharmaceutical composition containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These

excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the US Patents 4,256,108;4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules where in the active ingredient is mixed with an inert solid diluent, for example calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such a polyoxyethylene with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in

a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified, for example sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally- occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soya bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example gycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be in a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be

employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of formula (I) may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc containing the compounds of Formula (I) are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

Dosage levels of the order of from about 0.05 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above- indicated conditions (about 2.5 mg to about 7 gms per patient per day). for example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day (about 0.5 mg to about 3.5 gms per patient per day).

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy. The following non-limiting Examples are intended to illustrate the preparation of compounds of Formula (1), and as such are not intended to limit the invention as set forth in the claims appended thereto.

In the Examples, the following abbreviations are used:

RT Room temperature

EDC 1-(3-Dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride

TNFα Tumour necrosis factor α

ELISA Enzyme linked immunosorbent assay

LPS Lipopolysaccharide (Endotoxin)

Intermediate 1 3-Phthalimidopropanaldehyde diethylacetal

A solution of potassium phthalmide (2g, 10.8 mmol) and 3-bromopropanaldehyde diethylacetal (1.8g, 10.8 mmol) in dry dimethylformamide (20ml) was heated at 110°C for 2h. The mixture was allowed to cool then partitioned between ethyl acetate (70ml) and water (20ml). The organic extract was washed with water (3x20ml), dried ($MgSO_4$) and evaporated *in vacuo* to provide the title compound as a while solid (2.99g, 84%).

Tlc: EtOAc/hexanes (1:4), R_f 0:43

Intermediate 2 3-Phthalimidopropanaldehyde

A solution of intermediate 1 (2.5g, 9.2 mmol) in ethanol (15ml) and 1M hydrochloric acid (15ml) was heated under reflux, then ethanol distilled off until the distillation head temperature reached 99°C. The separated oil was then extracted into dichloromethane (2x25ml), the combined extracts dried ($MgSO_4$) and evaporated *in vacuo* to provide the title compound as a while solid (1.7g, 92%).

Tlc: EtOAc/hexanes (1:4), R_f 0.03

Similarly prepared was:-

Intermediate 3 2-Phthalimidoacetaldehyde

From commercially available 2-phthalimidoacetaldehyde diethylacetal, as a white solid (2.1 g; 99%).

Tlc: EtOAc/hexane (1:4), R_f 0.10

Intermediate 4 3-Phthalimidopropyl-L-leucyl-L-phenylalanine*N*-methylamide

Sodium triacetoxyborohydride (911mg, 4.3 mmol) was added in a single portion to a stirred solution of L-leucyl-L-phenylalanine-N-methyl amide (500mg, 1.72 mmol) and intermediate 2 (348mg, 1.72 mmol) in dry 1,2-dichloroethane (20ml). The mixture was stirred at room temperature for 1 hour before a further portion of sodium triacetoxyborohydride (500mg, 2.4 mmol) was added. After a further 1 hour the mixture was diluted with dichloromethane (50ml), washed with

saturated sodium bicarbonate (2x30ml), dried ($MgSO_4$) and evaporated *in vacuo* to provide a yellow foam.

Purification by column chromatography eluting with 5% methanol in dichloromethane provided the product as a white solid (711mg, 87%).

Tlc: 5%MeOH/CH_2Cl_2, R_f 0.18

Similarly prepared were:-

Intermediate 5 2-Phthalimidoethyl-L-leucyl-L-phenylalanine *N*-methylamide

From intermediate 3, as a white solid (159mg; 98%)

Tlc: 5% MeOH-0.1% Et_3N-CH_2Cl_2, R_f 0.35

Intermediate 6 *N*-(Methoxycarbonyl)methyl-L-leucyl-L-phenylalanine *N*-methylamide

From commercially available methyl glyoxalate mono-methylacetal, as a near white solid (780mg; 58%).

Tlc: EtOAc/CH_2Cl_2 (1:1), R_f 0.17

Intermediate 7 2-(1,1-Dimethylethyl)mercaptoethyl-L-leucyl-L-phenylalanine *N*-methylamide

From 2-(1,1-dimethylethyl)mercaptoacetaldehyde, as a pale yellow foam (310mg, 41%).

Tlc: EtOAc/CH_2Cl_2 (1:1), R_f 0.17

Intermediate 8 *N*-(3-Phthalimidopropyl)-L-valinyl-L-phenylalanine *N*-methylamide

From intermediate 2 (0.73 g, 3.61 mmol) and L-valinyl-L-phenylalanine *N*-methylamide, as a white solid (489 mg, 29 %).

Tlc: (5 % MeOH/CH_2Cl_2), R_f 0.23

Intermediate 9 *N*-[1,1-Dimethylethyl)sulphanylacetyl]-*N*-(methoxycarbonyl)methyl-L-leucyl-L-phenylalanine *N*-methylamide

From intermediate 6 and 2-(1,1-dimethylethyl)mercaptoacetic acid according to the procedure outlined for example 1, as a colourless foam. (370mg, 61%).

Tlc: EtOAc/CH_2Cl_2 (1:1), R_f 0.42.

Intermediate 10 *N*-(Methoxycarbonyl)methyl-*N*-(2-nitrophenylsulphanyl-sulphanyl)acetyl-L-leucyl-L-phenylalanine *N*-methylamide

A solution of intermediate 9 (360mg, 0.73mmol) in glacial acetic acid (5ml) was treated with 2-nitrosulphenyl chloride (140mg, 0.74mmol). The mixture was then stirred at room temperature for 3h. The solvent was evaporated *in vacuo* and the semi-solid residue purified by column chromatography eluting with 40% ethyl acetate in dichloromethane providing the title compound (310mg, 72%) as a yellow solid.

Tlc: EtOAc/CH_2Cl_2 (1:1), R_f 0.17

Intermediate 11 *N*-(Methoxycarbonyl)ethyl-L-leucyl-L-phenylalanine *N*-methylamide

A solution of L-leucyl-L-phenylalanine *N*-methylamide (1.09 g) in ethanol (20 ml) was treated with methyl acrylate (0.33 ml). The resulting colourless solution was heated to 70 °C over 7.5 h. The crude product was purified by flash silica chromatography, eluting with ethyl acetate/methanol (9:1) to provide the title compound was isolated as a white solid (0.482 g).

Tlc: EtOAc/MeOH (9:1), R_f 0.74

Intermediate 12 *N*-(Methoxycarbonyl)propyl-L-leucyl-L-phenylalanine *N*-methylamide

A solution of L-leucyl-L-phenylalanine *N*-methylamide (1.19 g) in ethanol (24 ml) was treated with methyl 4-iodobutyrate (0.93 g); the resulting colourless solution was heated to 45 °C over 16 h. The crude product was purified by flash silica chromatography, eluting with ethyl acetate/heptane (1:1 to 5:1), to furnish the title compound as an off-white solid (0.42 g).

Tlc: EtOAc/MeOH (9:1), R_f 0.41

Intermediate 13 *N*-Phthalimidomethyl-L-leucyl-L-phenylalanine *N*-methylamide

A solution of L-leucyl-L-phenylalanine *N*-methylamide (1.3 g) in dichloromethane (13 ml) was treated with *N*-bromomethylphthalimide (1.17 g) and sodium iodide (0.06 g). The resulting yellow solution was stirred at room temperature for 16 h. The solution was treated with saturated sodium bicarbonate solution (ca. 8 ml) and extracted with dichloromethane. The crude, organic extracts were preadsorped onto silica gel and purified by flash silica chromatography, eluting

with ethyl acetate/heptane (5:1), to furnish the title compound as a white solid (0.74 g).

Tlc: EtOAc, R_f 0.46

Intermediate 14 *N*-Hydroxy-L-leucine 1,1-dimethylethyl ester

Was prepared according to the procedure of Grundke *et al* in *Synthesis* 1987, 1115.

Intermediate 15 *N*-Chloroacetyl-*N*-hydroxy-L-leucine 1,1-dimethylethyl ester

Chloroacetyl chloride (0.32 ml) was added to a solution of intermediate 14 (0.80 g, 4.2 mmol) in tetrahydrofuran (10 ml) containing solid sodium bicarbonate (600 mg) at 0°C. The mixture was stirred at 0°C to room temperature for 3 h, then diluted with dichloromethane (100 ml) and washed with sat. sodium bicarbonate, 1N hydrochloric acid and brine, dried ($MgSO_4$) and evaporated *in vacuo* to give a colourless solid residue. Purification by column chromatography eluting with ether/hexanes (1:3) gave the title compound as colourless crystalline solid (1.10 g, 94 %).

TLC R_f 0.29 (ether/hexanes 1:3).

Intermediate 16 *N*-Acetylsulphanylacetyl-*N*-hydroxy-L-leucine 1,1-dimethylethyl ester

Potassium thioacetate (0.90 g) was added to a solution of intermediate 15 (1.10 g, 3.9 mmol) in methanol at RT. The mixture was stirred for 2 h, then evaporated *in vacuo*. The resiude was dissolved in dichloromethane, washed with water and brine, dried ($MgSO_4$) and evaporated *in vacuo* to give an orange oil. Purification by column chromatography eluting with hexane/ether (2:1) provided the title compound as colourless solid (0.80 g, 64 %).

TLC R_f 0.22 (2:1 hexane/ether).

Intermediate 17 *N*-Acetylsulphanylacetyl-*N*-hydroxy-L-leucine

Trifluoroacetic acid (10 ml) was added to a solution of intermediate 16 (0.80 g, 2.5 mmol) in dichloromethane (10 ml) at RT and the mixture stirred for 2 h. The solvent was then evaporated and residual trifluoroacetic acid removed by azeotropic distillation with hexanes to provide the title compound as colourless viscous oil (0.60

TLC R_f 0.05 (ether/hexane

Example 1 *N*-Acetylsulphanylacetyl-*N*-(3-phthalimidopropyl)-L-leucyl-L-phenylalanine *N*-methylamide

Acetylsulphanylacetic acid (310mg, 2.31mmol) was dissolved in thionyl chloride (0.3ml, 4.1mmol) and the mixture stirred for 15 minutes. Excess thionyl chloride was then evaporated *in vacuo* to provide an orange oil.

A solution of the intermediate acid chloride in dry dichloromethane (1ml) was added dropwise at 0°C to a stirred solution of intermediate 4 (372mg, 0.78mmol) and triethylamine (0.4ml, 2.88 mmol) in dry dichloromethane (10ml). The mixture was then stirred at room temperature overnight. The mixture was diluted with dichloromethane (50ml) and the solution washed sequentially with 8% sodium bicarbonate (2x30ml), 2M hydrochloric acid (2x30ml), water (30ml) and brine (30ml), dried ($MgSO_4$) and evaporated *in vacuo* to a brown solid.

Purification by column chromatography eluting with ethyl acetate/dichloromethane (1:1) provided the product as a white solid (320mg, 68%).

Tlc: EtOAc/CH_2Cl_2 (1:1), R_f 0.06

Similarly prepared was:-

Example 2 *N*-Acetylsulphanylacetyl-*N*-(2-phthalimidoethyl)-L-leucyl-L-phenylalanine *N*-methylamide

From intermediate 5, as a near white solid (98 mg; 52%).

Tlc: EtOAc/CH_2Cl_2 (6:4) R_f 0.27

Example 3 *N*-Acetylsulphanylacetyl-*N*-[2-(1,1-dimethylethyl)mercapto]ethyl-L-leucyl-L-phenylalanine *N*-methylamide

From intermediate 7, as a pale yellow oil (530mg; 63%).

Tlc: EtOAc/CH_2Cl_2 (1:1), R_f 0.26

Example 4 *N*-Acetylsulphanylacetyl-*N*-[2-(Methoxycarbonyl)ethyl]-L-leucyl-L-phenylalanine *N*-methylamide

A solution of intermediate 11 (0.448 g) in ethyl acetate (5 ml) at room temperature was treated with acetylsulphanylacetic acid (0.239 g), *N*-methylmorpholine (0.6 ml), propylphosphonic anhydride (1.314 g of a 50% solution in ethyl acetate) and *N,N*-dimethylaminopyridine (0.015 g). The resulting yellow solution was stirred at room temperature over 48 h. A deep brown solution resulted which was washed with 2N aqueous hydrochloric acid (ca. 5 ml) and saturated

sodium bicarbonate solution (ca. 5 ml), and extracted with ethyl acetate. The crude product was purified by flash silica chromatography, eluting with ethyl acetate/heptane (3:1), to give the title compound as a pale yellow oil (0.486 g).

Tlc: EtOAc, R_f 0.74

Example 5 ***N*-Acetylsulphanylacetyl-*N*-[2-(methoxycarbonyl)propyl]-L-leucyl-L-phenylalanine *N*-methylamide**

A solution of intermediate 12 (0.42 g) in dichloromethane (10 ml) was treated with thioacetic acid (0.22 g) followed by EDAC.HCl (0.23 g). The resulting yellow solution was stirred at room temperature for 16 h. The crude product was preadsorped onto silica gel and purified by flash silica chromatography, eluting with ethyl acetate/heptane (1:1 to 2.3:1), to furnish the title compound as a white solid (0.35 g).

Tlc: EtOAc, R_f 0.51

Example 6 ***N*-Acetylsulphanylacetyl-*N*-hydroxy-L-leucyl-L-phenylalanine *N*-methylamide**

Intermediate 17 (0.60 g, 2.5 mmol) and phenylalanine *N*-methylamide (0.60 g, 1.35 eq.) were dissolved in tetrahydrofuran at 0 °C and EDC (0.48 g) and *N*-hydroxybenzotriazole (0.34 g) were added. The resulting mixture was stirred at RT for 3 h, then evaporated *in vacuo*. The residue was dissolved in dichloromethane, washed with sat. sodium bicarbonate, 0.5 N hydrochloric acid and brine, dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was purified by column chromatography eluting with ethyl acetate to give the title compound, as colourless glass (0.62 g, 56 %).

TLC R_f 0.42 (EtOAc)

Example 7 ***N*-(3-Phthalimidopropyl)-*N*-sulphanylacetyl-L-leucyl-L-phenylalanine *N*-methylamide**

A solution of example 1 (150mg, 0.25mmol) in anhydrous methanol (3ml) was treated at 5°C with sodium methoxide (150mg, 0.26mmol) and the mixture stirred for 2h. The mixture was poured into dichloromethane (20ml) and the solution washed sequentially with 2M hydrochloric acid (2x10ml), water (10ml) and brine [illegible] dried ($MgSO_4$) and evaporated [illegible] off white solid (128mg, 92%).

Tlc: EtOAc/CH_2Cl_2 (1:1) R_f 0.18

Similarly prepared were:-

Example 8 *N*-Sulphanylacetyl-*N*-(2-phthalimidoethyl)-L-leucyl-L-phenylalanine *N*-methylamide

From example 2, as a near white solid (47mg; 77%).

Tlc: MeOH/CH_2Cl_2 (5:95), R_f 0.39

Example 9 *N*-Sulphanylacetyl-*N*-hydroxy-L-leucyl-L-phenylalanine *N*-methylamide

From example 6, as a colourless foam (89%)

TLC R_f 0.38 (EtOAc)

Intermediate 18 *N*-Acetylsulphanylacetyl-*N*-[2-(2-nitrophenyl)sulphanyl-sulphanylethyl]-L-leucyl-L-phenylalanine *N*-methylamide

A solution of intermediate 10 (190mg, 0.34 mmol) in glacial acetic acid (5ml) was treated with 2-nitrophenylsulphenyl chloride (80mg, 0.42 mmol) and the mixture stirred at room temperature for 3h. The solvent was evaporated *in vacuo* and the semi-solid residue purified by column chromatography eluting with ethyl acetate/hexane (1:1) providing the title compound (350mg, 94%) as a bright yellow solid.

Tlc: EtOAc/CH_2Cl_2 (1:1), R_f 0.21

Example 10 *N*-(2-Acetylsulphanylethyl)-*N*-sulphanylacetyl-L-leucyl-L-phenylalanine *N*-methylamide

A solution of intermediate 18 (250mg, 4.03 mmol) in a mixture of methanol (3ml) and chloroform (10ml) was treated at 0°C with sodium borohydride (76mg, 1.97 mmol) and the mixture allowed to warm to room temperature over 0.5h . The mixture was then washed sequentially with water (10ml), 1M hydrochloric acid (10ml), water (10ml) and brine (10ml) before drying ($MgSO_4$) and evaporating *in vacuo* to provide the product as an off-white solid (175mg; 97%).

Tlc: EtOAc/CH_2Cl_2 (1:1), R_f 0.24

Example A

Collagenase inhibition activity

The potency of compounds of general formula (I) to act as inhibitors of collagenase was determined by the procedure of Cawston and Barrett, (Anal. Biochem., 99:340-345, 1979) whereby a 1mM solution of the inhibitor being tested or dilutions thereof was incubated at 37°C for 16 hours with collagen and collagenase

(buffered with 50 mM Tris, pH 7.6 containing 5 mM $CaCl_2$, 0.05% Brij 35, 60 mM NaCl and 0.02% NaN_3). The collagen was acetylated ^3H or ^{14}C-collagen prepared by the method of Cawston and Murphy (Methods in Enzymology, 80:711, 1981). The choice of radiolabel did not alter the ability of collagenase to degrade the collagen substrate. The samples were centrifuged to sediment undigested collagen and an aliquot of the radioactive supernatant removed for assay on a scintillation counter as a measure of hydrolysis. The collagenase activity in the presence of 1mM inhibitor, or a dilution thereof, was compared to activity in a control devoid of inhibitor and the results reported as that inhibitor concentration effecting 50% inhibition of the collagenase (IC_{50}).

Example B

Stromelysin inhibition activity

The potency of compounds of general formula (I) to act as inhibitors of stromelysin was determined using the procedure of Nagase et al (Methods in Enzymology Vol 254, 1994), whereby a 0.1 mM solution of the inhibitor being tested or dilutions thereof was incubated at 37°C for 16 hours with stromelysin and ^3H transferrin (buffered with 50 mM Tris, pH 7.6 containing 10 mM $CaCl_2$, 150M NaCl, 0.05% Brij, 35, and 0.02% NaN_3). The transferrin was carboxymethylated with ^3H iodoacetic acid. The stromelysin activity in the presence of 1 mM, or a dilution thereof, was compared to activity in a control devoid of inhibitor and the results reported as that inhibitor concentration effecting 50% inhibition of the stromelysin (IC_{50})

Example C

Gelatinase inhibition activity

The potency of the compounds of general formula (I) to act as inhibitors of gelatinase was determined using the procedure of Harris & Krane (Biochem Biophys. Acta, 258:566 - 576, 1972), whereby a 1 mM solution of the inhibitor being tested or dilutions thereof was incubated at 37°C for 16 hours with gelatinase and heat denatured ^3H or ^{14}C-acetylated collagen (buffered with 50 mM Tris, pH 7.6 containing 5 mM $CaCl_2$, 0.05% Brij 35 and 0.02% NaN_3). The ^3H or ^{14}C gelatin was prepared by denaturing ^3H or ^{14}C collagen produced according to the method of Cawston and Murphy (Methods in Enzymology, 80:711, 1981) by incubation at 60°C

for 30 minutes. Undigested gelatin was precipitated by addition of trichloroacetic acid and centrifugation. The gelatinase activity in the presence of 1 mM, or dilution thereof, was compared to the activity in a control devoid of inhibitor and results reported as that inhibitor concentration effecting 50% inhibition of the gelatinase (IC_{50}).

Example D

MMP Inhibition Activity-Fluorimetric Assay

The potency of compounds of general formula (I) to act as inhibitors of collagenase-1(MMP-1), collagenase-2 (MMP-8), gelatinase-A (MMP-2), gelatinase-B (MMP-9) and stromelysin-1(MMP-3) was determined using the following procedure: Inhibitors are dissolved in dimethylsulphoxide containing 0.02% b-mercaptoethanol and serial dilutions are prepared. Activated enzyme is incubated in assay buffer containing 50mM Tris, pH 7.4, 5mM $CaCl_2$, 0.002% NaN_3 and Brij 35 in the presence and absence of inhibitor. Samples are preincubated at 37°C for 15 minutes before the addition of the fluorimetric substrate (Mca-Pro-Leu-Dpa-Ala-Arg-NH_2) to a final concentration of 10mM. The assay is incubated for 90 minutes at 37°C and then read in a Fluoroscan II at l_{ex} (355nm) and l_{em} (460nm).

The enzyme activity was compared to activity in a control devoid of inhibitor and the results reported as that inhibitor concentration effecting 50% inhibition of the stromelysin (IC_{50}).

Example E

Inhibition of TNFα production

The potency of the compounds of general formula (I) to act as inhibitors of the production of TNFa was determined using the following procedure. A 1mM solution of the inhibitor being tested or dilutions thereof was incubated at 37° C in an atmosphere of 5% CO_2 with THP-1 cells (human monocytes) suspended in RPM1 1640 medium and 20μM β-mercaptoethanol at a cell density of 1 x 10^6/ml and stimulated with 5μg/ml final concentration of LPS. After 18 hours the supernatant is assayed for the levels of TNFα using a commercially available ELISA kit (R & D Systems). The activity in the presence of 0.1mM inhibitor or dilutions thereof

was compared to activity in a control devoid of inhibitor and results reported as that inhibitor concentration effecting 50% inhibition of the production of TNFa.

Example F

Adjuvant arthritic rat model

Compounds of general formula (I) were evaluated in an adjuvant arthritis model in the rat based on the methods employed by B.B. Newbould (1963), Br.J.Pharmacol, 21, 127-136 and C.M. Pearson and F.D. Wood (1959), Arthritis Rheum, 2, 440-459. Briefly male Wistar rats (180-200g) were injected at the base of the tail with Freund's adjuvant. Twelve days later the responding animals were randomised into experimental groups. Compounds of general formula (I) were dosed either orally as a suspension in 1% methyl cellulose or intraperitoneally in 0.2% carboxymethylcellulose from day 12 to the end of the experiment on day 22. Hind paw volumes were measured every two days from day 12 onwards and X-rays were taken of the hind feet on completion of the experiment. Results were expressed as the percent increase of foot volume over day 12 values.

Example G

Mouse ovarian carcinoma xenograft model

Compounds of general formula (I) were evaluated in an ovarian carcinoma xenograft model of cancer, based on that described by B. Davies et al (1993), Cancer Research, 53, 2087-2091 This model, in brief, consists of inoculating female nu/nu mice with 1 x 10^9 OVCAR3-icr cells into the peritoneal cavity. Compounds of general formula (I) are administered by the oral route as a suspension in 1% methyl cellulose or intraperitoneally as a suspension in phosphate buffered saline in 0.01% Tween-20. At the conclusion of the experiment (4-5 weeks) the number of peritoneal cells are counted and any solid tumour deposits weighed. In some experiments tumour development is monitored by measurement of tumour specific antigens.

Example H

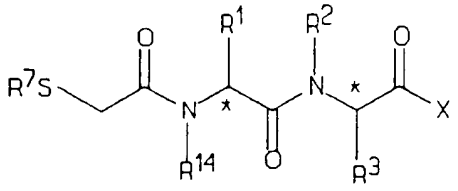
Rat mammary carcinoma model

Compounds of general formula (I) were evaluated in a HOSP.1 rat mammary carcinoma model of cancer (S Eccles et al (1995) Cancer Research, in press). This model consists of the intravenous inoculation of female CBH/cbi rats with 2 x 10^6

tumour cells into the jugular vein. Compounds of general formula (I) are administered by the oral route as a suspension in 1% methyl cellulose or intraperitoneally as a suspension in phosphate buffered saline in 0.01% Tween-20. At the conclusion of the experiment (4-5 weeks) the animals were killed, the lungs were removed and individual tumopurs counted after 20 hours fixation in Methacarn.

CLAIMS

1. Compounds of general formula (I)



(I)

wherein:

R^1 is a C_{1-6} alkyl, C_{2-6} alkenyl, (C_{1-6} alkyl) aryl, aryl, (C_{1-6} alkyl) heteroaryl, heteroaryl or C_{1-6} alkyl AR^9 group where A is O, NR^9 or $S(O)_m$ where m=0-2, and R^9 is H, C_{1-4} alkyl, aryl, heteroaryl, C_{1-4} alkyl-aryl or C_{1-4} alkyl-heteroaryl; if A=NR^9 the R^9 groups may be the same or different.

R^2 is hydrogen or C_{1-6} alkyl;

R^3 is a $[Alk]_nR^6$ group where Alk is a C_{1-6} alkyl or C_{2-6} alkenyl group and n is zero or 1;

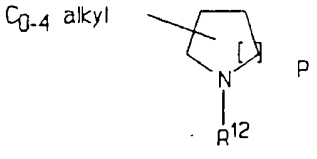
X is a group NR^4R^5 where R^4 is hydrogen, aryl, heteroaryl, C_{1-6} alkyl-heteroaryl, cyclo(C_{3-6})alkyl, C_{1-6} alkyl-cyclo(C_{3-6})alkyl, heterocyclo(C_{3-6})alkyl or C_{1-6} alkyl-heterocyclo(C_{3-6})alkyl, or the group C_{1-6} alkyl optionally substituted by amino (NH_2), aryl, arylamino, protected amino, di (C_{1-6} alkyl) amino, mono (C_{1-6} alkyl) amino, CO_2H, protected carboxyl, carbamoyl, mono (C_{1-6} alkyl) carbamoyl, di (C_{1-6} alkyl) carbamoyl, and R^5 is hydrogen or a C_{1-6} alkyl group; or NR^4 R^5 forms a ring;

R^7 is hydrogen or the group R^{10} CO where R^{10} is a group C_{1-4} alkyl, C_{1-4} alkyl-aryl, C_{1-4} alkyl- heteroaryl, cyclo (C_{3-6}) alkyl, C_{1-4} alkyl-cyclo (C_{3-6}) alkyl, C_{2-6} alkenyl, C_{2-6} alkenyl-aryl, aryl or heteroaryl;

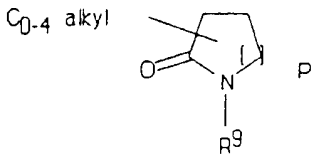
R^{14} is OH, NH_2, OR^8, NHR^8 or R^8;

R^8 is aryl (optionally substituted with R^{11}), heteroaryl (optionally substituted with R^{11}), C_{1-4} alkyl (optionally substituted with R^{11}), C_{1-4} alkyl-aryl (optionally substituted with R^{11}), C_{1-4} alkyl-heteroaryl (optionally substituted with R^{11}), C_{2-6} alkenyl

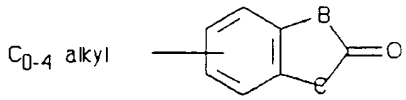
(optionally substituted with R^{11}), cyclo (C_{3-6}) alkenyl (optionally substituted with R^{11}), C_{1-4} alkyl-cyclo (C_{3-6}) alkyl (optionally substituted with R^{11}), the groups



or



where p=1-2, or the group



where B and C may be selected from the groups $O,S,C(R^9)_2$, or NR^9 and these may be the same or different;

R^6 is an optionally substituted cyclo(C_{3-6}) alkyl, cyclo(C_{3-6}) alkenyl, C_{1-6} alkyl, aryl, C_{1-6} alkoxyaryl, benzyloxyaryl, heteroaryl, COR^9, C_{1-3} alkyl-aryl, C_{1-3} alkyl-heteroaryl, alkyl-CO_2R^9, C_{1-6} alkyl-NHR^9, AR^9, CO_2R^9, $CONHR^{10}$, $NHCOR^{10}$, $NHCO_2R^{10}$ or $NHSO_2R^{10}$ group, an amidine or guanidine group;

R^{11} is SR^7, COR^{13}, SO_2R^9 (when R^9 is not H), $SO_2N(R^9)_2$, $N(R^9)_2$, NR^9R^{12}, OR^9, COR^9, phthalimido or succinimido;

R^{12} is hydrogen, COR^9, CO_2R^9, $CONHR^9$ or SO_2R^9 (where R^9 is not H); and

R^{13} is OH, OC_{1-4} alkyl, $O(C_{1-4}$ alkyl)-aryl or $N(R^9)_2$ (in which R^9 is the same or different);

and the salts, solvates and hydrates thereof.

2. A compound of claim 1, where R^1 is C_{1-6} alkyl or C_{1-4} alkyl-AR^9 where A is $S(O)_m$, NR^9 or O and m=0,1 or 2, and R^9 is H, C_{1-4} alkyl, heteroaryl or aryl.

3. A compound of any preceding claim, where R^2 is H or C_{1-4} alkyl.

4. A compound of any preceding claim, where R^3 is $[Alk]_nR^6$ where n=0 or 1, Alk is C_{1-4} alkyl and R^6 is C_{1-4} alkyl, C_{1-3} alkyl-aryl, C_{1-3} alkyl-heteroaryl, AR^9,

CO_2R^9, $CONHR^{10}$, $NHCOR^{10}$, $NHCO_2R^{10}$ or $NHSO_2R^{10}$, an amidine or guanidine group.

5. A compound of any preceding claim, where R^5 is H.

6. A compound of any preceding claim, where R^4 is H, C_{1-6} alkyl, aryl, heteroaryl, C_{1-6} alkyl-aryl, C_{1-6} alkyl-heteroaryl or C_{1-4} alkyl-$N(R^9)_2$.

7. A compound of any preceding claim, where NR^4R^5 is a 5-7 membered ring.

8. A compound of claim 7, wherein NR^4R^5 is pyrrolidine, piperidine or morpholine.

9. A compound of any preceding claim, where R^7 is H or $R^{10}CO$ where R^{10} is C_{1-4} alkyl or aryl.

10. A compound of any preceding claim, where R^8 is C_{1-4} alkyl-R^{11}, C_{1-4} alkenyl-R^{11}, cyclo(C_{3-6})alkyl-R^{11} or C_{1-4} alkyl.

11. A compound of any preceding claim, where R^{11} is COR^{13}, NR^9R^{12}, $N(R^9)_2$, phthalimido or succinimido.

12. A compound of any preceding claim, where R^{12} is COR^9, CO_2R^9 (provided R^9 is not H), or SO_2R^9 (provided R^9 is not H).

13. A compound of any preceding claim, where R^{13} is OH, OC_{1-4} alkyl or $N(R^9)_2$.

14. A compound of any preceding claim, where R^{14} is OH or R^8.

15. A compound of claim 1, wherein R^{14} is R^8 and R^4 is H or optionally-substituted alkyl.

16. A compound of claim 1, selected from

N-Acetylsulphanylacetyl-*N*-(3-phthalimidopropyl)-L-leucyl-L-phenylalanine *N*-methylamide

N-Acetylsulphanylacetyl-*N*-(2-phthalimidoethyl)-L-leucyl-L-phenylalanine *N*-methylamide

N-Acetylsulphanylacetyl-*N*-[2-(1,1-dimethylethyl)sulphanylethyl]-L-leucyl-L-phenylalanine *N*-methylamide

N-Acetylsulphanylacetyl-*N*-[2-(methoxycarbonyl)ethyl]-L-leucyl-L-phenylalanine *N*-methylamide

N-sulphanylacetyl-*N*-(2-phthalimidoethyl)-L-leucyl-L-phenylalanine *N*-

N-(2-Acetylsulphanylethyl)-*N*-sulphanylacetyl-L-leucyl-L-phenylalanine *N*-methylamide.

17. A compound of claim 1, selected from

N-Acetylsulphanylacetyl-*N*-[2-(methoxycarbonyl)propyl]-L-leucyl-L-phenylalanine *N*-methylamide and

N-(3-Phthalimidopropyl)-*N*-sulphanylacetyl-L-leucyl-L-phenylalanine *N*-methylamide.

18. A compound of claim 1, selected from

N-Acetylsulphanylacetyl-*N*-hydroxy-L-leucyl-L-phenylalanine*N*-methylamide and

N-Sulphanylacetyl-*N*-hydroxy-L-leucyl-L-phenylalanine *N*-methylamide.

19. A compound of any preceding claim, in the form of a single enantiomer or diastereomer, or a mixture of such isomers.

20. A pharmaceutical composition for use in therapy, comprising a compound of any preceding claim, and a pharmaceutically-acceptable diluent or carrier.

21. Use of a compound of any of claims 1 to 19, for the manufacture of a human or veterinary medicament for the treatment or prevention of a condition associated with matrix metalloproteinases or that is mediated by TNFα.

22. Use according to claim 21, wherein the condition is selected from cancer, inflammation and inflammatory diseases, tissue degeneration, periodontal disease, ophthalmological disease, dermatological disorders, fever, cardiovascular effects, haemorrhage, coagulation and acute phase response, cachexia and anorexia, acute infection, HIV infection, shock states, graft versus host reactions, autoimmune disease, reperfusion injury, meningitis and migraine.

23. Use according to claim 21, wherein the condition is selected from tumour growth, angiogenesis, tumour invasion and spread, metastases, malignant ascites and malignant pleural effusion.

24. Use according to claim 21, wherein the condition is selected from rheumatoid arthritis, osteoarthritis, osteoporosis, asthma, multiple sclerosis, neurodegeneration, Alzheimer's, stroke, vasculitis, Crohn's disease and ulcerative colitis.

25. Use according to claim 21, wherein the condition is selected from corneal ulceration, retinopathy and surgical wound healing.

26. Use according to claim 21, wherein the condition is selected from psoriasis, atopic dermatitis, chronic ulcers and epidermolysis bullosa.

27. Use according to claim 21, wherein the condition is selected from periodontitis and gingivitis.

28. Use according to claim 21, wherein the condition is selected from rhinitis, allergic conjunctivitis, eczema and anaphylaxis.

29. Use according to claim 21, wherein the condition is selected from atherosclerosis and congestive heart failure.

INTERNATIONAL SEARCH REPORT

Internat ul Application No
PCT/GB 96/01138

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K5/062 A61K38/05

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,95 06031 (IMMUNEX CORP) 2 March 1995 see claims; examples ---	1-15, 19-29
A	WO,A,88 06890 (RES CORP TECHNOLOGIES INC) 22 September 1988 see claims; examples ---	1-15, 19-29
A	EP,A,0 273 689 (BEECHAM GROUP PLC) 6 July 1988 see claims; examples ---	1-15, 19-29
A	EP,A,0 126 974 (SEARLE & CO) 5 December 1984 cited in the application see claims; examples --- -/--	1-15, 19-29

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search	Date of mailing of the international search report
25 September 1996	18.10.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Fuhr, C

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO,A,95 13289 (CHIROSCIENCE LTD ;MONTANA JOHN (GB); DICKENS JONATHON (GB); OWEN D) 18 May 1995 see claims; examples ---	1-15, 19-29
P,A	WO,A,96 11209 (CHIROSCIENCE LTD) 18 April 1996 see claims; examples ---	1-29
X	WO,A,94 22491 (DIAGNOSTIKFORSCHUNG INST ;ERBER SEBASTIAN (DE); DINKELBORG LUDGER) 13 October 1994 see claim 11 -----	1

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat' Application No
PCT/GB 96/01138

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9506031	02-03-95	AU-A-	7569494	21-03-95
		EP-A-	0715619	12-06-96
		FI-A-	960803	22-04-96
		NO-A-	960723	23-02-96
WO-A-8806890	22-09-88	AT-T-	106087	15-06-94
		DE-D-	3889726	30-06-94
		DE-T-	3889726	13-10-94
		EP-A-	0358660	21-03-90
		JP-T-	2502537	16-08-90
EP-A-0273689	06-07-88	AU-B-	599736	26-07-90
		AU-A-	8292687	01-09-88
		CA-A-	1322073	07-09-93
		DE-A-	3774858	09-01-92
		IE-B-	60751	10-08-94
		JP-A-	63215660	08-09-88
		US-A-	4937243	26-06-90
		US-A-	5109000	28-04-92
EP-A-0126974	05-12-84	AU-B-	575048	21-07-88
		AU-A-	2722284	22-11-84
		CA-A-	1284850	11-06-91
		DE-A-	3472108	21-07-88
		JP-B-	6045635	15-06-94
		JP-A-	59205350	20-11-84
		JP-A-	6316594	15-11-94
		US-A-	4511504	16-04-85
WO-A-9513289	18-05-95	AU-A-	8113394	29-05-95
		EP-A-	0728144	28-08-96
		NO-A-	961888	09-05-96
WO-A-9611209	18-04-96	AU-A-	3612795	02-05-96
WO-A-9422491	13-10-94	DE-A-	4311021	27-10-94
		AU-A-	6501594	24-10-94
		CA-A-	2156618	13-10-94
		EP-A-	0692979	24-01-96
		HU-A-	72733	28-05-96

INTERNATIONAL SEARCH REPORT

...ormation on patent family members

Interna ...l Application No
PCT/GB 96/01138

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9422491		NO-A- 953865	23-11-95

Structure 1

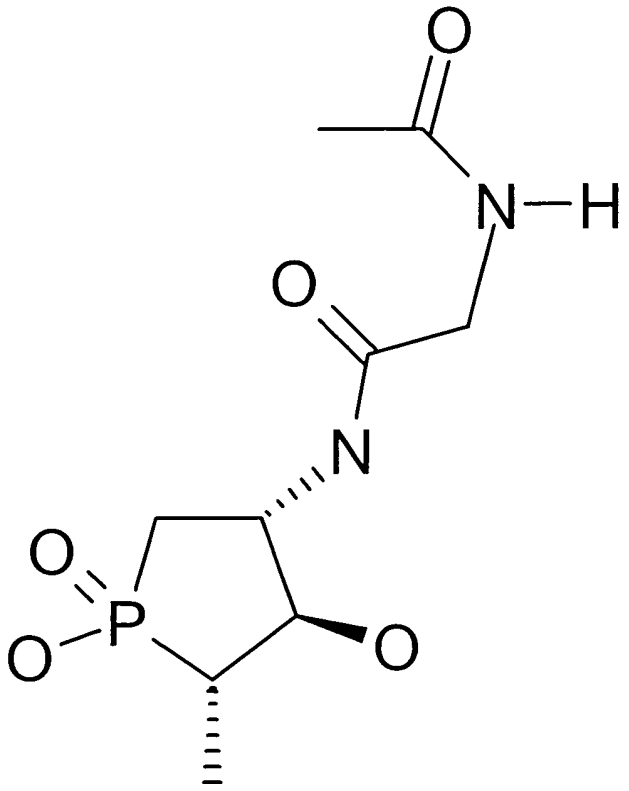

FIG. 2

Structure 2

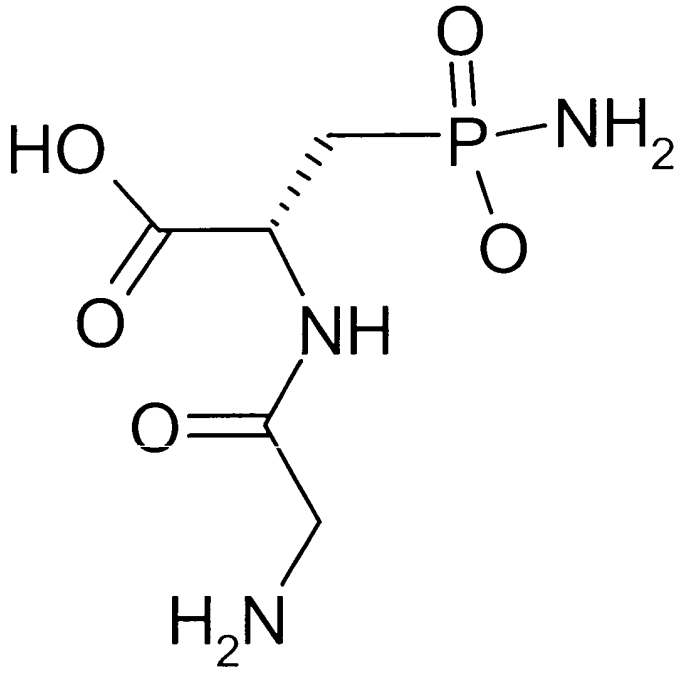

FIG. 3